Notice of Allowability	Application No.	Applicant(s)	
	09/927,121	GOLD ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 12/22/03; 3/23/04; 3/30/04
2. ☑ The allowed claim(s) is/are 83-103 RENUMBERED 1-21
3. ☐ The drawings filed on _____ are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☑ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☑ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☑ Examiner's Amendment/Comment
8. ☑ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

PHILLIP GAMBEL
Phillip Gambel
Primary Examiner 5/4/04
Art Unit: 1644
TECH CENTER 1600

DETAILED ACTION

1. Applicant's amendment, filed 12/22/03, is acknowledged.

Claims canceled: 1-16 and 18-60.

Claims added: 61-82.

Claims pending: 17 and 61-82.

Claim 17 stands withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement on 5/9/03.

Claims 61-82 *are under consideration in the instant application.*

2. Applicant's IDSs, filed 4/3/02, 12/22/03, 3/11/04 and 3/16/04 are acknowledged.

3. The Declarations of Dr. Gold and Dr. Uhr, filed 12/22/03 under 37 C.F.R 1.132, are acknowledged.

EXAMINER'S AMENDMENT

4. An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to Applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the Issue Fee.

5. Authorization for this Examiner's Amendment was given in telephone interviews with Jeffrey W. Guise and Russell T. Boggs on 3/23/04, and with Russell T. Boggs on behalf of Jeffrey W. Guise on March 30, 2004.

In the Specification

6. The paragraph at page 18, line 9 through page 19, line 10 has been amended as follows:

The novel baculovirus/insect cell expression system has proven effective for the efficient production of functional antibodies for immunotherapy from any given patient. This baculovirus expression vector was designed such that only two custom gene-specific primers were needed to amplify any pair of antibody variable regions for easy subcloning and expression as human kappa light chain and $IgG_{\gamma 1}$ heavy chain. The incorporation of heterologous secretory ~~secretary~~ signal sequences, which directed the heavy and light chains to the secretary pathway, were incorporated for the expression of large amounts of active immunoglobulin from insect cells. This vector should be useful for the expression of any kappa light chain variable region (V_L) in frame with human kappa constant region and secreted via the human placental alkaline phosphatase secretory ~~secretary~~ signal sequence; and any heavy chain variable region (V_H) in frame with the human $IgG_{\gamma 1}$ constant domain led by the honey bee melittin secretory ~~secretary~~ signal sequence. In other systems, the lambda light chain constant region replaces the kappa constant region. The chimeric protein is then expressed with the V_L region in frame with human lambda constant region and secreted via the human placental alkaline phosphatase secretory ~~secretary~~ signal sequence, along with any heavy chain variable region (V_H) in frame with the human $IgG_{\gamma 1}$ constant domain led by the honey bee melittin secretory ~~secretary~~ signal sequence. Any monoclonal antibody, mouse or human, either from a monoclonal cell line or identified by phage display cloning, could be easily expressed as whole human $IgG_{\gamma 1}/\kappa$ or $IgG_{\gamma 1}/\lambda$ in this vector after two simple subcloning steps. Additionally, different immunoglobulin types, including $IgG_{\gamma 2}$, $IgG_{\gamma 3}$, $IgG_{\gamma 4}$, IgA, IgA, IgA_1, IgA_2, IgM, IgD, IgE heavy chains, or segments thereof, could be used in place of $IgG_{\gamma 1}$. Furthermore, besides those signal sequences described *supra*, the instant invention may use other secretory signal sequences such as the endogenous secretory sequences associated with the immunoglobulin genes derived from a given patient. Additionally, one of skill in the art would be able to select several different primers that could be used equivalently in this system to produce equivalent results to amplify any pair of antibody variable regions for easy subcloning.

In The Claims

7. Claims 1-82 have been canceled.

8. The following new claims have been added:

-- 83. A method for treating a B cell mediated malignancy in a patient, said method comprising: administering to said patient a composition comprising two chimeric proteins; wherein

(1) the first chimeric protein comprises at least a portion of a V_H region and at least a portion of an immunoglobulin constant region,

(2) the second chimeric protein comprises at least a portion of a V_L region and at least a portion of an immunoglobulin constant region,

(3) wherein said V_H and said V_L region are isolated from a malignant B cell clone from said patient having said B cell mediated malignancy; and

(4) wherein said chimeric proteins are produced in insect cells by a baculovirus expression vector wherein

(a) the gene encoding said first chimeric protein is operatively linked to an AcNPV p10 promoter and a honey bee melittin secretory signal sequence, or is operatively linked to an AcNPV polyhedrin promoter and a human placental alkaline phosphatase secretory signal sequence; and

(b) the gene encoding said second chimeric protein is operatively linked to an AcNPV p10 promoter and a honey bee melittin secretory signal sequence, or is operatively linked to an AcNPV polyhedrin promoter and a human placental alkaline phosphatase secretory signal sequence;

and

wherein said first and said second chimeric proteins are not operatively linked to the same promoter.

84. The method of claim 83 wherein said V_H or V_L region is an entire variable region.

85. The method of claim 83 wherein said second chimeric protein comprises an immunoglobulin constant region comprising a human kappa or lambda constant region.

86. The method of claim 83 wherein said first chimeric protein comprises an immunoglobulin constant region selected from the group consisting of a human $IgG_{\gamma 1}$ constant region, a human $IgG_{\gamma 2}$ constant region, a human $IgG_{\gamma 3}$ constant region, a human $IgG_{\gamma 4}$ constant region, a human IgA_1 constant region, a human IgA_2 constant region, a human IgM constant region, a human IgD constant region, and a human IgE constant region.

87. The method of claim 86 wherein said first chimeric protein comprises an immunoglobulin constant region comprising a human $IgG_{\gamma 1}$ constant region.

88. The method of claim 83 wherein said chimeric proteins are conjugated to a carrier protein.

89. The method of claim 88 wherein said carrier protein is a keyhole-limpet hemocyanin (KLH).

90. The method of claim 83 wherein said composition is further co-administered with a cytokine or chemokine.

91. The method of claim 90 wherein said cytokine is granulocyte-macrophage-colony stimulating factor (GM-CSF).

92. The method of claim 83 wherein said first and second chimeric proteins comprise a protein comprising said V_H region and a human $IgG_{\gamma 1}$ constant region and a protein comprising said V_L region and a human kappa or lambda chain constant region.

93. The method of claim 83 wherein said insect cells are *Trichoplusia ni* or *Spodoptera frugiperda* (Sf9) cells.

94. The method of claim 83 wherein said chimeric proteins are analyzed for expression by ELISA.

95. The method of claim 83 wherein said chimeric proteins are isolated using a protein selected from the group consisting of protein A, protein G, protein L and other proteins being able to bind to an immunoglobulin binding domain.

96. The method of claim 83 wherein said other protein able to bind an immunoglobulin binding domain is an anti-immunoglobulin antibody.

97. The method of claim 83 wherein said B cell mediated malignancy is a B cell lymphoma.

98. The method of claim 97 wherein said B cell lymphoma is refractory low grade lymphoma or follicular B cell lymphoma.

99. The method of claim 83 wherein the gene encoding a chimeric protein comprising a V_L region and an immunoglobulin constant region is controlled by said polyhedrin promoter in said baculovirus expression vector, and the gene encoding a chimeric protein comprising a V_H region and an immunoglobulin constant region is controlled by said p10 promoter in said baculovirus expression vector.

100. The method of claim 83 wherein the gene encoding a chimeric protein comprising a V_L region and an immunoglobulin constant region is controlled by said polyhedrin promoter in said baculovirus expression vector.

101. The method of claim 83 wherein the gene encoding a chimeric protein comprising a V_H region and an immunoglobulin constant region is controlled by said p10 promoter in said baculovirus expression vector.

102. The method of claim 83 wherein the gene encoding a chimeric protein comprising a V_L region and an immunoglobulin constant region is operatively linked to said human placental alkaline phosphatase secretory signal sequence in said baculovirus expression vector.

103. The method of claim 83 wherein the gene encoding a chimeric protein comprising a V_H region and an immunoglobulin constant region is operatively linked to said honey bee melittin secretory signal sequence in said baculovirus expression vector. --

REASONS FOR ALLOWANCE

9. The following is an Examiner's Statement of Reasons for Allowance:

The Examiner's Amendment set forth supra, in conjunction with Applicant's amendment filed 12/22/03, has obviated the previous rejections of record by limiting the independent claim to a method in which the chimeric proteins administered are produced using an expression vector having a combination of specific promoters and secretory signal sequences. Although the individual promoters and secretory signal sequences were known in the art, Applicant argues that the ordinary artisan would not have been motivated to select this particular combination and the Examiner concurs.

Accordingly, the instant claims are deemed allowable.

10. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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March 30, 2004